REMARKS

Applicant respectfully requests reconsideration. Claims 50, 52-53, 55-57, 59-60, 62-64, 66-70, 72-86 and 97-102 were previously pending in this application. No claims are amended herein. As a result, claims 50, 52-53, 55-57, 59-60, 62-64, 66-70, 72-86 and 97-102 are still pending for examination with claims 50, 57, 64, 70, 77 and 82 being independent claims. No new matter has been added.

Rejection Under 35 U.S.C. 112

Applicants thank the Examiner for the indication that the rejection for a lack of written description has been withdrawn.

Claims 50, 52-53, 55-57, 59-60, 62-64, 66-70, 72-86 and 97-102 have been rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

In particular, the Examiner has reviewed the evidence presented by Applicant and concluded that such evidence was not persuasive to overcome the rejection under 35 U.SC. §112 as lacking enablement. In particular, the Examiner has concluded that the "Applicant has not taught or shown the skilled artisan in the art how to harness the immunostimulatory activities to render it therapeutic in the manner relating to the claimed invention." (Office Action page 3-4). A number of reasons were provided in support of that conclusion, each of which Applicant will address below. However, in general the Examiner is arguing that the art was unpredictable and the data provided in the specification was not sufficient to teach the skilled artisan how to use the claimed invention. Applicant disagrees.

The data provided in the specification identified a new class of compounds, CpG oligonucleotides, for treating disease. It was discovered that oligonucleotides containing an unmethylated CpG dinucleotide were able to mimic the response in a host to bacterial infection. As described in the specification a normal immune response to bacterial infection arises as a result of bacteria breaking apart and releasing DNA into the body. Such DNA is recognized by the immune system and results in the promotion of an immune response that leads to the attack on the invading pathogen. The inventors taught that unmethylated CpG oligonucleotides when administered to a

host were recognized by the host as a bacterial infection, causing the induction of an immune response sufficient to kill an invading pathogen. When CpG oligonucleotides are administered to an infected host the host mounts an immune response to the infection.

The data provided in the specification and discussed in prior responses to Office Action, were sufficient to establish

1. that CpG oligonucleotides were a class of therapeutic agent and

2. that these new therapeutics functioned in a manner similar to bacteria such that they caused induction of a robust immune response in a host capable of treating an infectious disease.

In response to the enablement rejection Applicant previously submitted publications that were published prior to the invention establishing a nexus between various aspects of the immune response and the treatment of viral infections. The papers were presented for the purpose of establishing what was known by the skilled artisan at the time of the invention. That is, the skilled artisan recognized that induction of certain immune factors was useful for treating viral infection. The skilled artisan would have known and understood that CpG oligonucleotides were useful in the treatment of infectious disease, including viral infections. Applicants address below each of the additional points raised by the Examiner in the Office Action.

Pages 7-24 of the Office Action are identical to the prior Office Action, with the exception of the last paragraph on page 14. Applicant previously addressed each of these arguments in the prior responses to office action. Applicant reiterates those arguments here. However, rather than repeating all of Applicant's arguments, Applicant asks the Examiner to refer to the prior response where each point was addressed.

On Page 3 of the Office Action it is stated that "As provided in the previous Office Actions, it is known in the art that these oligonucleotides induce a TH1 biased immune response, which produces TH1 associated cytokines, and that the induction of a TH1 immune response is also important to resolving infections." As stated in the prior responses, Applicant strongly disagrees with this statement. It was not known in the prior art that these oligonucleotides induce a TH1 biased immune response. This is part of Applicant's invention. Applicant was the first to discover that oligonucleotides containing an unmethylated CpG dinucleotide functioned to produce a robust immune response. It is not possible to consider the enablement of the claimed invention if the

Office is improperly considering part of the invention as being part of the prior art. The data provided in the specification related to immune induction, including TH1 cytokines, was data generated in support of the invention.

It is further stated that "However, the art that a balance between a TH1 and TH2 immune response is of importance in resolving infections; see teachings of Infante-Duarte et al." (Office Action page 3). It is believed that the Examiner is referring to Infante-Duarte et al., Springer Seminars in Immunopathology, 1999, 21:317-338. This reference does not form part of the prior art, but rather was published several years after Applicant's priority date.

It is further stated that "Applicant had failed to set forth any guidance as to the type and level of immune profile that the oligonucleotides must ascertain in order to render it therapeutically effective." (Office Action page 4). It is further questioned what level of B cells and NK cells as well as cytokines are necessary to treat viral infections and it is noted that Krieg et al., Annu. Rev. Immunol., 2002, Vol. 20, 709-760 teaches that oligonucleotides have distinct immune profiles. The skilled artisan reviewing the data and patent application would have expected that oligonucleotides having an unmethylated CpG motif would have the ability to induce an immune response that would be useful in protecting the body against infectious disease. The variability observed with different oligonucleotides containing CG relates to optimization. It would require only routine experimentation for the skilled artisan to identify a CpG oligonucleotide useful in the claimed methods in view of the teaching found in the specification. For instance, the skilled artisan could select an oligonucleotide described in the specification.

On Page 5 it is concluded that "It should further be noted that in the years following Applicant's filing of the claimed invention, the art still has not recognize the use of CpG oligonucleotides as an active ingredient in treating, preventing and ameliorating HBV infection. At the very most, the art acknowledges the use of these oligonucleotides as an adjuvant in vaccines." (Office Action Page 5). A number of papers published since Applicant's invention by a number of different research groups have described studies of CpG oligonucleotides in the treatment of HBV infection. For instance, two papers describe use of CpG oligonucleotides without coadministration of an antigen (Li N et al APMIS. 2005 Oct;113(10):647-54 & Li N et al Immunol Lett. 2006 Jan 15;102(1):60-6.). Li N et al 2005 describes a study examining Anti-HBV effects of CpG

oligodeoxynucleotide-activated peripheral blood mononuclear cells (PBMCs) from patients with chronic hepatitis B. The authors found that the secretion of IFN-α by CpG ODN-activated PBMCs from chronic hepatitis B patients and healthy controls was significantly increased when compared with PBMCs alone or GpC ODN-stimulated PBMCs. Treatment of HepG2 2.2.15 cells with culture supernatants of PBMCs activated by CpG ODN was shown to significantly reduce secretion of HBV specific proteins and DNA. The authors concluded that their "results indicated that CpG ODN could efficiently enhance the immune response of chronic hepatitis B patients." Li N et al 2006 demonstrated the inhibition of HBV replication in vitro by a CpG oligodeoxynucleotide. The authors concluded that "These results suggest that CpG ODN can inhibit indirectly HBV replication in vitro via activating the immune cells, and could contribute to the development of an immunoregulator against HBV infection."

Applicants specification provided a teaching of a class of compounds that provided *in vitro* and *in vivo* data establishing the presence of a robust immune response and taught that such an immune response would be useful in the treatment of viral infections. The skilled artisan at the time of the invention would have recognized that this assertion was true based on the data and what was known in the art at the time of the invention. One skilled in the art would recognize the utility of treating viral infection based on the disclosure and data provided in the instant patent application. Applicants have provided examples in the specification that show production of antibody in response to oligonucleotide stimulation (Example 2), stimulation of B cells, natural killer (NK) cells and monocytic cells (Example 3, Example 4, Example 11, Figure 6 and Figure 11), and production of IFNγ (Figure 15) as well as other cytokines.

The relation between IFNγ and treatment of viral infections was studied by Morris et al. (Infection and Immunity, 1982, 35(2):533-536) who showed that IFNγ is produced from two human T-lymphoblastoid lines upon virus infection (see page 536, left column). Baumgarth et al. (Journal of Virology, 1994, 68(11):7575-7581) disclose that IFNγ has been identified as a key factor in immune responses to viral infections and demonstrated IFNγ production in response to influenza virus. Following the invention those of skill in the art, recognizing the utility of this class of therapeutics, based on the disclosure of the instant inventors, and following the guidance provided

in the specification, demonstrated as the Applicant had taught that CpG oligonucleotides were useful for treating viral infection.

The references are not cited to demonstrate that prior to the invention CpG oligonucleotides were useful for treating viral or HBV infections. Rather, these references are cited to establish what was known in the art at the time of the invention regarding a correlation between immune stimulation and the treatment of viral infection. The purpose of the references is to establish that a known relationship existed between the immune response produced by CpG oligonucleotides (and shown in the specification) and the treatment of viral disorders.

The skilled artisan would not need to test numerous parameters to identify an oligonucleotide useful for treating viral infection. The specification provides a number of species which induce an immune response. The skilled artisan could select from any of these species or, using routine experimentation, could identify other species and test for activity as described in the specification. The routine nature of these selections is evidenced by papers published following the invention which involve the selection of a CpG oligonucleotide and the demonstration that it was useful in treating viral infections.

On Page 6 of the Office Action Applicant's arguments regarding the different issues in enablement for administration of a cytokine and a CpG oligonucleotide are addressed. It is asserted that the issues are similar and that like a cytokine CpG oligonucleotides may throw off the balance of immune factors leading to problems and side effects and in particular that induction of a Th1 biased response would necessarily achieve this. It is further stated that arguments cannot take the place of evidence.

Applicant directs the Office's attention to the evidence provided in the specification. In paragraphs 142-143 of the published application it is taught that

> [0142] Vertebrate DNA is highly methylated and CpG dinucleotides are under represented. However, the stimulatory CpG motif is common in microbial genomic DNA, but quite rare in vertebrate DNA. In addition, bacterial DNA has been reported to induce B cell proliferation and immunoglobulin (Ig) production, while mammalian DNA does not (Messina, J. P. et al., J. Immunol. 147:1759 (1991)). Experiments further described in Example 3, in which methylation of bacterial DNA with CpG methylase was found to abolish mitogenicity, demonstrates that the difference in CpG

status is the cause of B cell stimulation by bacterial DNA. *This data supports the following conclusion: that unmethylated CpG dinucleotides present within bacterial DNA are responsible for the stimulatory effects of bacterial DNA.*

[0143] *Teleologically, it appears likely that lymphocyte activation by the CpG motif represents an immune defense mechanism that can thereby distinguish bacterial from host DNA. Host DNA, which would commonly be present in many anatomic regions and areas of inflammation due to apoptosis (cell death), would generally induce little or mo lymphocyte activation due to CpG suppression and methylation. However, the presence of bacterial DNA containing unmethylated CpG motifs can cause lymphocyte activation precisely in infected anatomic regions, where it is beneficial.* This novel activation pathway provides a rapid alternative to T cell dependent antigen specific B cell activation. Since the CpG pathway synergizes with B cell activation through the antigen receptor, B cells bearing antigen receptor specific for bacterial antigens would receive on e activation signal through cell membrane Ig and a second signal from bacterial DNA, and would therefore tend to be preferentially activated. The interrelationship of this pathway with other pathways of B cell activation provide a physiologic mechanism employing a polyclonal antigen to induce antigen-specific responses. (emphasis added)

The cited paragraphs provide the rational for the functioning of CpG oligonucleotides based on the data provided in the specification. Based on all the data in the specification, the authors provide an explanation of how the CpG oligonucleotides are functioning. It has been demonstrated that CpG oligonucleotides are functioning in a manner similar to bacterial DNA. When the host tissue is exposed to bacterial DNA an immune response is provoked by the host which is designed to attack and kill invading microorganisms. It was discovered by the instant inventors that such a response could be mimicked by using synthetic DNA having the properties of bacterial DNA, namely unmethylated CpG dinucleotides. The CpG oligonucleotides provoke a Th1 biased immune response, unlike many other immune stimulators that provoke a Th2 biased immune response, which can have detrimental effects on the body. A Th1 biased immune response is one that is naturally produced by the body in response to exposure to bacterial DNA or synthetic CpG oligonucleotides. It is quite different than administering a single cytokine. A single cytokine may have positive effects on the host but the administration must be such that the amounts are carefully controlled to produce positive physiological results. This is quite different than a CpG

oligonucleotide which is recognized by the host and then the host produces the immune response and change in cytokines levels.

On pages 14-15 of the Office Action Applicant's arguments regarding Equils et al, Agrawal et al and Olbrich et al are addressed. It is asserted that Applicant taught that these references were enabling for the invention. It is requested that Applicant's arguments be reconsidered. The argument that Applicant was presenting was that the references should be considered in their entirety. While the references teach limitations in using CpG oligonucleotides they also teach of the advantages of using CpG oligonucleotides. Any drug, even FDA approved drugs, have limitations on their use. Applicant's point is that specific sentences cannot be pulled from the references to support the lack of enablement of the therapeutic use of CpG oligonucleotides. The teachings must be considered in their entirety. When the references are considered in their entirety, they support the therapeutic use of CpG oligonucleotides in the treatment of viral infection, while at the same time recognizing a few drawbacks or limitations that require optimization. Such optimization does not require undue experimentation. It is something that researchers perform on all drugs and therapeutic methods.

Double Patenting Rejection

Claims 50, 52-53, 55-57, 59-60, 62-64, 66-70, 72-86 and 97-102 have been provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 59-61, of copending Application No. 11/255,100.

Claims 59-61 of US Application No. 11/255,100 have been withdrawn as being part of a non-elected invention. Claims 59-61 will be canceled in response to the outstanding office action. Therefore it is requested that the rejection be withdrawn.

Claims 50, 52-53, 55-57, 59-60, 62-64, 66-70, 72-86 and 97-102 have been provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 19-33, of copending Application No. 10/987,146.

US Application No. 10/987,146 has been abandoned. Therefore it is requested that the rejection be withdrawn.

CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Dated: September 8, 2008

Respectfully submitted,

By 

Helen C. Lockhart
Registration No.: 39,248
WOLF, GREENFIELD & SACKS, P.C.
Federal Reserve Plaza
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
617.646.8000